LISTE DES ABREVIATIONS

PAC: Pneumopathie aiguë communautaire

CAP: Community-acquired pneumonia

ICS: Inhaled corticosteroids

SPE: Simple pleural effusion

LDH: Lactate deshydrogenase

CPE: Complicated pleural effusion

COPD: Chronic obstructive pulmonary disease

SCS: Systemic corticosteroids

NSAID: Non steroids anti-inflammatory drug

CRP: C reactive protein

PaO_2: Arterial oxygen tension

$PaCO_2$: Arterial carbon dioxide tension

E: Empyema

NE: No empyema

SD: Standart deviation

OR: Odds ratio

CI: Confidence intervals

ICU: Intensive care unit

IL: Interleukine

TNF-α: Tumour necrosis factor-α

Plan

Introduction

La pneumopathie aiguë communautaire est la sixième cause de mortalité en France. Sa prise en charge nécessite une hospitalisation dans 15 à 20 % des cas. Il s'agit d'une infection du parenchyme pulmonaire d'évolution aiguë, acquise en milieu extra-hospitalier ou survenant avant la 48ème heure d'admission à l'hôpital. Lorsque son étiologie est retrouvée, l'agent pathogène le plus fréquemment identifié est le *Streptococcus pneumoniae*, associé à un taux de mortalité de 14 à 16 %. Malgré les recommandations clairement définies sur la prise en charge des pneumopathies, elles sont toujours à l'origine d'un nombre important de décès chaque année (11 000 décès en 2011 selon le bulletin épidémiologique hebdomadaire).

L'empyème ou épanchement pleural purulent est défini pas la constitution d'un dépôt de fibrine dans l'espace pleural. Son analyse est caractérisée par un aspect macroscopiquement purulent, la présence de polynucléaires neutrophiles, un pH < 7,2, des lactates déshydrogénases > 1000 UI/L, ou une culture bactériologique positive. Sa prise en charge nécessite une antibiothérapie prolongée, des procédures de soins invasives (ponctions pleurales, drainage, parfois chirurgie thoracique) et une durée d'hospitalisation plus longue. Tous ces facteurs ont une répercussion en terme de coûts d'hospitalisation et en font un problème de santé publique.

Il nous a donc paru intéressant de rechercher les différents facteurs associés à la présence d'un empyème afin d'identifier, dès leur admission, les patients à risque de complications et d'optimiser leur prise en charge.

Pour réaliser notre étude, nous avons recensé, avec la participation du DIM (Département d'Informations Médicales), les patients hospitalisés entre janvier 2006 et décembre 2010 pour une pneumopathie aiguë communautaire ou une pleurésie purulente dans le service de pneumologie du CHU d'Angers. Nous avons ensuite reporté la prise en charge initiale effectuée en ambulatoire, les antécédents médicaux et comorbidités, les traitements au long cours, les données cliniques, radiologiques, biologiques, microbiologiques de ces patients et la prise en charge hospitalière. Au total, 439 patients ont été inclus dans l'étude parmi lesquels 84 pleurésies purulentes ont été diagnostiquées. Il s'agit d'un des effectifs d'empyème les plus importants dans la littérature.

Article

INDEPENDANT FACTORS ASSOCIATED WITH EMPYEMA IN COMMUNITY-ACQUIRED PNEUMONIA.

Introduction

Community-acquired pneumonia (CAP) is one of the most frequent cause of hospitalisation and displays a high rate of mortality in industrialized country [1]. Parapneumonic effusion is the main complication of CAP (52%), whereas empyema remains rare (8%) [2]. Despite medical improvements, a retrospective study in United States described an increased rate of hospitalisation for empyema since 1996 related to increased incidence of *Staphylococcus aureus* infections [3]. Empyema is a frequent cause of early failure in the management of CAP[4], requiring most of the time invasive procedure and prolonged hospital stay, with an impact on health-care cost[5-8].

In few studies assessing predictive factors of complicated pleural effusion, age, alcohol and smoking abuse, intraveinuse drug use, and higher inflammatory markers at admission were shown to be independently associated with empyema [2, 9, 10]. However, these results were sometimes contradictory and no study assessed predictive factors specifically of empyema.

Recently, Sellares et al. demonstrated that prior inhaled corticosteroids (ICS) treatment decreased incidence of parapneumonic effusion in a population of patients hospitalised for CAP[11].

The main purpose of the present study was to identify baseline characteristics associated with empyema in patients admitted in hospital for CAP. Additionally, we aimed to assess the own effect of prior inhaled and systemic corticosteroids treatment on incidence of empyema.

Material and methods

Patients' selection and inclusion criteria

A retrospective study was carried out at university hospital in Angers, France. Medical informatic database was used to recruit patients hospitalised for CAP between January 2006 and December 2010 in respiratory diseases department, then patients' paper-based medical records were analysed. According to French legislation, the agreement of an ethic committee is not required for retrospective collection of data corresponding to current practice.

Pneumonia was defined by the presence of infiltrate on chest radiograph associated with clinical evidences: cough, sputum, chest pain, crackles and fever [6, 12].

Complicated parapneumonic effusion (CPE) was characterized by LDH > 1000 IU/L in pleural fluid without any other criteria for empyema.

Empyema was characterized by purulent macroscopic aspect with majority of degenerated neutrophils or positive pleural fluid culture [10, 13].

Simple parapneumonic effusion (SPE) was defined by a pleural fluid without criteria of CPE.

Exclusion criteria were: Age < 18 years, hospitalisation in the preceding 21 days to exclude nosocomial pneumonia, cerebrovascular diseases with significant sequelae or previous laryngological surgeries to exclude aspiration pneumonia.

Data Collection

We reported:

- demographic data (age, gender),
- comorbidities (diabete, alcohol abuse, intravenous drug use, chronic heart disease, chronic obstruction pulmonary disease (COPD), asthma, bronchiectasie, chronic liver disease, chronic renal disease, smoking),
- current treatment (especially systemic corticosteroids (SCS), ICS, others immunosuppressive therapies, which were considered as current treatment if administrated since at least 30 days),
- recent ambulatory treatment for CAP (general practitioner's consultation, nonsteroidal antiinflammatory drugs (NSAID), SCS, antibiotics),

- baseline clinical data (length of disease before hospitalisation, chest pain, crackles),
- baseline blood laboratory data (C-reactive protein (CRP), leukocytes, albumin, PaO_2, $PaCO_2$),
- radiological data (infiltrate or abscess, or pleural effusion on chest radiographies or thoracic tomographies),
- pleural laboratory data (macroscopic aspect of pleural fluid, LDH, neutrophils count),
- microbiological data (blood, sputum, bronchioloalveolar lavage and pleural fluid cultures, and urinary antigen detection test for *Streptococcus pneumonia* and *Legionella pneumophila*),
- complications (length of hospital stay, intensive care unit admission (ICU), mortality),
- management of empyema during hospitalisation (antibiotic therapies, thoracocentesis, fibrinolytic use, pleural drainage, thoracic surgery).

Patients were categorized according to previous definitions into two groups: the first one "E" containing empyema, the second one "NE" (non empyema) containing CAP associated or not with pleural effusion without any criteria of empyema.

Statistical analysis

All statistical analyses were performed with SAS software (SAS/STAT Package 2002–2003 by SAS Institute Inc., Cary, NC, USA). The primary dependent variable of interest was the presence of empyema. Patients with and without empyema were compared using Chi-square test for categorical variables or Fisher's exact test when at least one cell frequency was less than 5. 2-sample t-test was used for continuous variables. Variables with p value < 0.05 were then entered in a logistic procedure with forward stepwise regression analysis in order to determine variables independently associated with the presence of empyema. Results were expressed as mean, standard deviation (SD) and adjusted odds ratio (OR) (95% confidence intervals (CI)). A 2-tailed probability value < 0.05 was considered significant.

Results

Population's characteristics

A total of 439 patients with CAP were included in this study. Among 181 patients with pleural effusion on chest radiography, 121 were explored by thoracocentesis. We identified 20 SPE (4.5%) and 101 CPE (23%) including 84 empyemas following aforementioned criteria (19% of all CAP). The flow chart of patients is represented on Figure 1.

Demographic data and comorbidities are shown in Table 1. In group E, patients were significantly younger, with more frequent alcohol abuse, but less frequent cardiac disease. We observed no difference in any other comorbidity especially on COPD and tobacco status.

Regarding current treatment, summarized in Table 2, ICS and SCS were significantly more frequent in group E, whereas we observed no difference in frequency of recent treatment with SCS or NSAID in both groups, neither in other current immunosuppressive therapy. Patients in group E had been more frequently treated with antipneumococcal antibiotics before hospitalisation.

Baseline patient’s characteristics

Clinical, biological and radiological characteristics are shown in Table 3. Inflammatory markers (CRP and leukocytes) at admission were significantly higher in patients of group E. We also observed a longer length of disease prior hospitalisation, and chest pain was more frequent at admission in this group. Empyema was associated with more frequent pulmonary abscess and loculated effusion. However, there was no difference in blood gases at hospital admission.

Microbiologic diagnosis was positive in 205 cases, as shown in Table 4. *Streptococcus pneumonia* was the most frequent agent isolated in both groups, identified either in pleural fluid (n=14), blood cultures (n=39), sputum (n=4), or by urinary antigen (n=84).

Hospital management

Empyema was associated to an early failure of management, requiring often an antibiotic adjustment. Indeed, 53,5 % of patients in group E needed an antibiotic adaptation, against only 39.5 % of group NE (p=0.025).

With regard to empyema management, all patients had thoracocentesis, 52 had pleural drainage (62 %), 23 had fibrinolytics use (27 %), and 7 needed thoracic surgery (8 %). Fibrinolytics use did not change significantly the length of hospital stay. Empyema was associated with a longer length of hospital stay (17.7 ± 11,8 days in group E, *vs* 10.9 ± 9,1 days in group NE, $p < 0.001$).

Between groups E and NE, we did not show any difference in term of mortality (respectively 1.2 % and 2.2 %) and ICU admission (respectively 14 % and 19 %).

Analysis of factors associated with empyema occurrence

Bivariate analysis revealed nine factors at hospital admission associated with empyema: younger age, alcohol abuse, absence of chronic heart disease, chest pain, CRP > 192 mg/L, leukocytes > 13000/mm^3, duration of symptoms before hospitalisation > 4 days, and current treatment with SCS and ICS.

In multivariate analysis, alcohol abuse, CRP > 192 mg/L, leukocytes > 13000/mm^3, length of disease before hospitalisation > 4 days remained significantly associated to empyema occurrence. Patients currently treated with SCS or presenting chronic heart diseases presented less empyema.

Discussion

In the present study, 439 patients were admitted for a CAP, and 84 developed empyema. The group E displayed showed a prolonged hospital stay but not higher mortality or ICU admission rate. In multivariate analysis, we identified four initial factors associated with empyema (alcohol abuse, longer length of disease before hospitalisation, higher initial CRP and leukocytes) whereas chronic heart disease and current treatment with SCS were associated with a significant decrease of empyema frequency.

We observed a rate of 19 % of empyema, which is in line with Voiriot et al. data[14]. However it is higher than other publications [9-11, 15], which is probably explained because empyema needs a specific management mainly delivered in respiratory diseases department and not in others departments. Thus there might be a bias of recruitment leading finally to a large sample of empyema cases.

We did not show any difference in term of mortality between groups E and NE. Chalmers and Cilloniz et al. found also comparable mortality rates between complicated pleural effusions or complicated pneumonias and pneumonias without pleural effusions [2, 9], whereas Falguera and Sellares et al., demonstrated a higher mortality in patients with CPE[10, 11].

In the present study, patients who developed empyema were younger and had more frequent chest pain, as described by other authors [2, 9, 10].

Multivariate analysis identified six initial factors associated with empyema. Increased baseline inflammatory biological markers had have already been demonstrated to be associated with empyema. Indeed, Chalmers et al. identified low serum albumin < 30g/l, elevated CRP > 100 mg/l and platelet count > $400X10^9$/l as predictors of complicated parapneumonic effusion or empyema [9], like other authors [2, 10]. As previously observed [10, 13] patients with empyema had a longer length of disease before hospitalisation. Alcohol abuse had been also described as predictive factors for empyema by Chalmers and Falguera et al. [9, 10]. Indeed, alcoholism has known to facilitate respiratory infections. In addition, these patients may have less recourse to health care professional with more frequent poor bucco-dental status, and could have a delayed treatment. Furthermore we showed that absence of chronic heart disease was significantly associated with empyema occurrence. We may suppose that this factor is linked to young age which was not significant anymore in multivariate analysis. Previously other studies identified also cardiac comorbidities and young age as protective for empyema in univariate analysis, and inversely to our study, only young age remained significantly protective in multivariate analysis [9, 10].

To our knowledge, for the first time our data suggested a protective effect of current SCS treatment on empyema occurrence. Effects of short term SCS treatment in the management of severe CAP have largely been studied. Despite controversial results about mortality, these works permitted to show that SCS decreased significantly pro-inflammatory cytokines (interleukine(IL)-6 and IL-8, Tumour necrosis factor-α (TNF-α)) and blood inflammatory markers (CRP and neutrophils)[16-18]. These data were confirmed in a study assessing lung infections in patients with long term SCS treatment [19]. Besides, Koegelenberg et al. described the pathogenesis of empyema [20]. The first stage of parapneumonic effusion was explained by increased pulmonary interstitial fluid traversing

pleura, associated to an increased vascular permeability in response to pro-inflammatory cytokines like IL-8 and TNF-α. Then, untreated exsudative effusions resulted in fibrinopurulent effusions, characterized by positive microbial culture and high concentration of neutrophils recruited via IL-8, associated with increased phagocytosis and cell lysis. Finally, there was a disturbance of physiological equilibrium between clotting and fibrinolysis, in which TNF-α is suspected to have a role by stimulating the release of Plasminogen Activator Inhibitors from mesothelial cells. Indeed, Aleman et al. showed increased Plasminogen Activator Inhibitor-2 in complicated pleural sepsis [21]. Thus, we can suppose that the attenuation of inflammatory response by SCS might prevent the formation of complicated parapneumonic effusion or empyema.

Unlike Voiriot et al. study, we could not find any link between recent NSAID treatment and the occurrence of empyema, which could be related to missing data about self-medication [14]. In the same way, ICS, that seemed as protective in bivariate analysis, had no effect anymore in multivariate analysis, inversely to Sellares et al. [11].

Limitations

This retrospective study displayed some missing data, especially about self-medication before hospitalisation. Secondly, we had no data about the different molecules of SCS, their dose and length of treatment. Therefore, we could not conclude about an eventual dose-response relationship between SCS and empyema occurrence. We were neither able to record exhaustively medical indications of current treatments with SCS, and thus, we could not measure the impact of these underlying pathways on empyema development. Thirdly, we displayed a bias of recruitment. Indeed, we included only patients hospitalised in respiratory diseases department, explaining a high rate of empyema, despite a smaller sample than in previous studies.

Conclusion

In summary, our study identified several patients baseline characteristics that were associated with empyema occurrence in patients admitted for CAP. This is the first study to our knowledge suggesting a protective effect of long term SCS treatment on empyema development.

Our results may have an interest to participate to the elaboration of a predictive score of empyema at admission to hospital, as previously proposed by Chalmers et al. [9].
Prospective studies, on larger samples of population, are necessary to confirm these results.

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Table des figures et des tableaux

Figure 1: Flow chart of study population

CAP: community acquired pneumonia; SPE: simple parapneumonic effusion; CPE: complicated parapneumonic effusion; LDH: lactates deshydrogenases

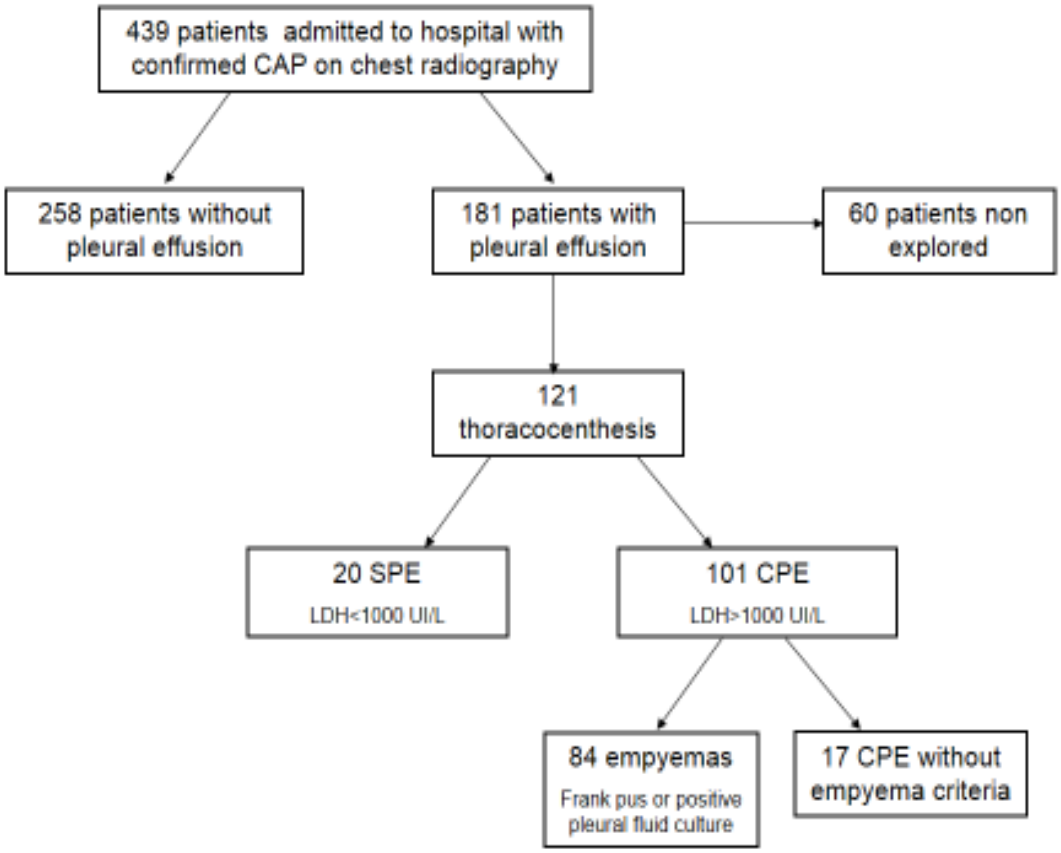


Table I. Population characteristics

COPD: chronic obstructive pulmonary disease; SD: standart deviation

	Empyema (n=84)	**No empyema (n=355)**	**P value**
Age, mean (SD)	59,2 ± 18,6	64,7 ± 20,5	0,023
Age < 60 years (%)	51,2	35,2	0,0067
Female (%)	45	44	NS
Tobacco (%)	56,0	51,7	NS
Diabete (%)	18,0	14,3	NS
Alcohol abuse (%)	30,1	11,2	<0,0001
Chronic heart disease (%)	15,6	32,3	0,0025
Broncho-pulmonary neoplasm (%)	8,3	3,6	NS
COPD (%)	13,2	18,8	NS
Asthma (%)	3,5	8,7	NS
Chronic liver disease (%)	4,7	1,6	NS
Chronic renal disease (%)	4,8	5,9	NS

Table II. Current and Recent treatments

NSAID: non steroidal anti-inflammatory drug; CAP: community-acquired pneumonia

	Empyema n=84	**No empyema** n=355	**P-value**
Current treatment:			
Inhaled corticosteroids (%)	4,8	18,5	0,021
Systemic corticosteroids (%)	2,4	11,2	0,0117
Chemotherapy (%)	2,3	4,2	NS
Other immuno-suppressive drugs (%)	1,2	3,9	NS
Recent ambulatory treatments for CAP			
NSAID (%)	10,6 (n=47)	11,4 (n=175)	NS
Systemic corticosteroids (%)	10,6 (n=47)	7,4 (n=175)	NS
Antibiotic therapy (%)	42,0 (n=69)	30,3 (n=326)	NS
Antibiotic therapy anti pneumococcal (%)	92 (n=25)	65,6 (n=96)	0,0049

Table III. Clinical, biological and radiological data

SD: standart deviation; CRP: C-reactive protein;
PaO_2: Arterial oxygen tension; $PaCO_2$: Arterial carbon dioxide tension

	Empyema	**No empyema**	**p-value**
Length of symptoms before hospitalisation, mean (SD)	9,20 ± 7,4 (n=77)	6,30 ± 6,2 (n=307)	0,0010
Chest pain at admission (%)	80,6 (n=31)	3€7,1 (n=342)	< 0,0001
Pulmonary abscess (%)	8,3 (n=84)	1,4 (n=355)	<0,005
Loculated effusion (%)	48,8 (n=84)	4,2 (n=355)	<0,001
CRP, mg/L, mean (SD)	262 ± 136,8 (n=80)	194 ± 136,0 (n=310)	< 0,0001
Leukocytes in blood, $x10^3/mm^3$, mean (SD)	16,4 ± 5,7 (n=82)	13,8 ± 6,5 (n=306)	0,0009
Albumin, g/L, mean (SD)	27 ± 0.86 (n=39)	32,2 ± 0.69 (n=101)	< 0,001
PaO_2, mmHg, mean (SD)	61.2 ± 2.4 (n=38)	61.03 ± 2.3 (n=184)	NS
$PaCO_2$, mmHg, mean (SD)	35.78 ± 0.87 (n=38)	36.4 ±0.51 (n=184)	NS

Table IV. Microbiology data

NE: No empyema group; E: Empyema group
Data are presented as number (percentage of total microbial positive diagnosis)

	NE N=108	**E N=42**	**p-value**
Gram positive cocci			
- *Streptococcus pneumoniae* (n=109)	87 (80,5)	22 (52,3)	NS
- *Staphyloccocus aureus* (n=6)	2 (1,8)	4 (9,5)	NS
- others (n=11)	1 (0,9)	10 (23,8)	NS
TOTAL	90 (83,3)	36 (85,6)	NS
Gram negative bacilli:			
- *Haemophilus influenzae* (n=3)	2 (1,8)	1 (2,3)	NS
- *Escherichia Coli* (n=2)	1 (0,9)	1 (2,3)	NS
- *Klebsiella spp* (n=1)	1 (0,9)	0	NS
- others (n=5)	2 (1,8)	3 (7,1)	NS
TOTAL	6 (5.5%)	5 (11.9%)	NS
Atypical agents:			
- *Legionella pneumophila* (n=12)	12 (11,1)	0	NS
- *Mycoplasma pneumonia* (n=1)	0	1 (2,3)	NS
TOTAL	12 (11.1%)	1 (2.3%)	NS

Table V. Multivariate analysis of factors associated with empyema

OR: odds ratio; CRP: C reactive protein

	OR	95% CI	p-value
Alcohol abuse	3,980	1,865-8,497	< 0,0001
Chronic heart disease	0,323	0,156-0,669	0,0025
Length of disease before hospitalisation > 4 days	2,716	1,385-5,327	< 0,0001
CRP > 192 mg/L	2,722	1,1413-5,247	< 0,0001
Leukocyte > $13x10^3/mm^3$	2,597	1,364-4,943	< 0,0001
Current systemic corticosteroids	0,179	0,037-0,856	0,0117

Conclusion

Cette étude a donc permis de mettre en évidence, de façon significative, différents facteurs à l'admission associés à la pleurésie purulente: l'exogénose chronique, un taux de marqueurs inflammatoires élevé, une durée d'évolution plus longue avant l'hospitalisation. Nous montrons également une incidence moindre d'empyème chez les patients porteurs d'une cardiopathie chronique ou traités par corticothérapie au long cours.

Concernant la prise en charge en soins primaires, plus de la moitié des patients hospitalisés pour une PAC avait bénéficié d'une consultation avec un médecin généraliste (67 %). Parmi ces patients, la moitié avait reçu une antibiothérapie. Celle-ci était à visée anti-pneumococcique dans la majorité des cas. Ces résultats sont en accord avec les récentes recommandations sur la prise en charge des PAC en ambulatoire. Par ailleurs, nous n'avons pas constaté de lien entre l'organisation des soins en ambulatoire et la survenue d'un empyème.

La possibilité d'un effet protecteur des corticoïdes oraux sur la survenue d'une pleurésie purulente dans les PAC est un des points importants de notre travail. Cependant, cette étude étant rétrospective, il existait des données manquantes concernant l'indication de la corticothérapie, le type de molécule, la posologie et la durée du traitement. Une étude prospective longitudinale permettrait de relever ces données de façon exhaustive et de mesurer leur influence. Un échantillon de population plus important permettrait également d'évaluer la sévérité de la présentation clinique et la mortalité chez les patients traités au long cours par corticothérapie. En effet, le nombre de décès dans l'étude n'était pas suffisant pour réaliser une analyse statistique.

Dans une récente étude, il a été démontré que les scores traditionnels clinico-biologiques de sévérité utilisés dans les PAC (PSI, CURB 65 score, CRB 65 score) n'étaient pas fiables pour estimer le risque de pleuropneumopathie compliquée ou d'empyème. Chalmers et al. proposent donc le calcul d'un score prédictif réalisable à l'admission du patient, basé sur les différents facteurs de risque mis en évidence dans leur étude. Un Score $\geq$ 2 apparaît avoir une bonne sensibilité (87 %) avec une valeur prédictive négative forte (98,5 %). L'identification des patients à risque de complications pleurales permettrait l'adaptation rapide de l'antibiothérapie (ciblée sur les germes cocci gram positif et anaérobies) ainsi que la recherche précoce d'épanchement par imagerie, notamment en cas de persistance du syndrome infectieux.

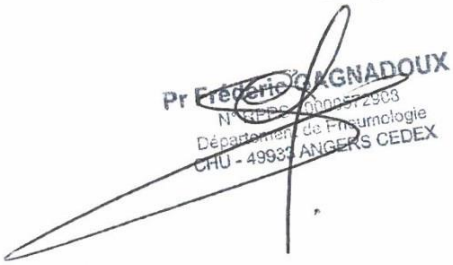
Table des matières

PERMIS D'IMPRIMER

THÈSE DE Madame GARREAU NOEMIE EPOUSE COULON

Vu, le Directeur de thèse

Vu, le Président du jury de thèse



Vu, le Doyen de la Faculté de Médecine d'ANGERS

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Résumé

Les pleurésies purulentes compliquant les pneumopathies aiguës communautaires (PAC) sont une cause importante d'échec de traitement et nécessitent souvent une prise en charge invasive avec un impact sur la durée d'hospitalisation et le coût des soins. L'objectif de l'étude était d'établir des facteurs à l'admission associés à la survenue d'un empyème.

Méthodes: Nous avons réalisé une étude rétrospective sur 439 patients hospitalisés pour une PAC dans le service de pneumologie du CHU d'Angers, entre janvier 2006 et décembre 2010. Les patients ont ensuite été classés en deux groupes selon la présence ou non d'une pleurésie purulente.

Résultats: Parmi les 439 PAC, 84 pleurésies purulentes ont été diagnostiquées (19 %). Les patients ayant un empyème étaient plus jeunes ($p = 0,023$), présentaient plus fréquemment une douleur thoracique à l'admission ($p < 0,0001$). Leur durée d'hospitalisation était significativement plus élevée ($p < 0,0001$). L'analyse multivariée a mis en évidence six facteurs associés à l'empyème. L'exogènose chronique ($p < 0,0001$), une durée d'évolution avant hospitalisation > 4 jours ($p < 0,0001$), un taux de CPR >192 mg/L ($p < 0,0001$) et un taux de leucocytes > 13000/mm^3 ($p < 0,0001$) à l'admission étaient associés à un risque plus élevé de survenue de pleurésie purulente. En revanche, l'existence d'une cardiopathie chronique ($p = 0,0025$) et la prise au long court de corticoïdes oraux ($p = 0,0117$) étaient associées à une diminution de la survenue de l'empyème.

Conclusion: Ces données ont permis d'identifier différents facteurs significativement associés à la pleurésie purulente. D'autres études prospectives seront nécessaires afin de confirmer nos résultats.

MOTS CLES

- Pneumopathie aigue communautaire
- Pleurésie purulente
- Empyème